Framework for Defining Evidentiary Standards for Biomarker Qualification:

LDL-C and HDL-C as Surrogate Endpoints

“The Good, the Bad, and the Ugly”

James Revkin, Pfizer
LDL-C / HDL-C Team
Framework for Defining Evidentiary Standards for Surrogate Endpoints
Biomarker Evidentiary Framework

In Drug Development

Need Statement
- CVD pre-eminent cause of global morbidity and mortality
- Hard Endpoints [CV death, non-fatal myocardial infarction, and non-fatal stroke (MACE)] requires:
  - Large numbers of subjects
  - BMx that predicts a treatment effect
  - Need to ID CV therapeutic agents for primary and secondary prevention

COU
- Level and Δ in serum LDL-C concentration as a predictive biomarker of CV risk long-term (5 year) rate of major coronary event outcomes
- Predict risk in 6 month trial with #subject related to event rate, and trial arm(s).
- All races, M/F, age 40-70

Factor likelihood and magnitude
- What is the acceptable level of uncertainty?
  - Informs Required Stringency of EC

Benefit
- Primary prevention
  - < deaths, stokes & acute MI
  - Early ID of CV risk and initiation of therapeutic interventions
- Secondary
  - Drive more aggressive therapeutics, address systemic vascular comorbidities
  - ID other mechanisms for reducing the risk of CV events

Risk
- Cholesterol level is only one of several CV risk factors
  - May not account for a Δ in risk for these other factors
  - A therapeutic that acts on one of the other factors will not be recognized as beneficial to CV event reduction

Evidentiary Criteria
- General
  - Cumulative LDL arterial burden is central determinant for initiation & progression of atherosclerotic CVD
  - Lower LDL-C level = > clinical benefit
- Surrogate Endpoint
  - Over decades of research has shown that multiple approaches to reducing LDL-C results in a reduction in CV events
  - Proportional (relative) risk reduction & absolute risk reduction relate to the magnitude of LDL-C reduction
  - Subsequently randomized clinical trials confirmed that the modification of levels of LDL-C could reduce the occurrence rate of major cardiovascular events.
Cardiovascular Risk Biomarker

**Epidemiology:**
- Since the mid-20th century, cardiovascular disease has been and remains the pre-eminent cause of global morbidity and mortality

**Gold standard:**
- Hard clinical endpoints: CV death, non-fatal myocardial infarction, and non-fatal stroke (MACE)

**Challenge:**
- Given that the ability to detect a treatment effect, i.e., the accrual of hard clinical endpoints, requires the recruitment of large numbers of subjects, the identification of a biomarker (circulating, imaging, or other) that predicts a treatment effect reliably, would enable a more rapid identification of new CV therapeutic agents for primary and secondary prevention
Historical Role of Cholesterol

Atheroma

Described by Albrecht Von Haller in 1755 as “a spongy tumor, a tumor and abscess enclosed in a thick membrane, with the consistency of pus.”

http://digital.ub.uni-duesseldorf.de/id/1886202

Rabbit aorta 124 days post cholesterol diet

Rabbit aorta 106 days post cholesterol diet followed by 785 days after reversion to normal chow diet

Dietary cholesterol responsible for atheromata

Demonstrated by Nikolai Anitschkow, 1913

Feeding rabbits cholesterol in suflower oil vs. Cholesterol alone.

Influences of lifestyle, genetics, diet on cholesterol levels and CV events

Studies initiated in 1953
- Conducted in 16 cohorts

- Cholesterol rose in proportion to the total fat intake ($r = 0.67$) and intake of saturated fatty acids ($r = 0.87$).

- Fatal coronary events rose in proportion to the serum cholesterol level ($r = 0.80$).

- In an evaluation of Japanese who moved eastward, there was a rise in cholesterol and an increase in mortality.

Influences of lifestyle, genetics, diet on cholesterol levels and CV events

Genetics and disorders of lipid metabolism

- 1938 C Müller described familial hypercholesterolemia as an “inborn error of metabolism” resulting in CV death
- 1964 Khachadurian described two forms of FH, hetero and homo-zygous
- 1974 Brown and Goldstein, by studying fibroblasts of FH subjects, revealed the role of HMG-Co-A reductase and LDL receptors in the regulation of cholesterol metabolism.
- 1987 Innerarity et al. described a mutation in Apo B-100 which had a low affinity for the LDL receptor, leading to hypercholesterolemia
- 1999 Varret et al described a distinct third genetic cause for autosomal dominant hypercholesterolemia, which was later attributed to a gain of function PCSK9 mutation


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1999 Varret et al described a distinct third genetic cause for autosomal dominant hypercholesterolemia, which was later attributed to a gain of function PCSK9 mutation
LDL- Cholesterol: History of Development

- Atherothrombotic disease is a cause of irreversible end organ injury
- Atheroma and the identification of cholesterol as a agent of atheroma burden
- Understanding the relationship between circulating cholesterol, lipoproteins, and atheroma burden
- The epidemiology revealing the relationship between cholesterol levels and cardiovascular (CV) events
- Discovery of modulators of levels of circulating cholesterol and different lipoproteins
  - LDL-receptor, SR-BI, and PCSK9
- The conduct of CV outcome studies showing that modulating levels of LDL-C impacts CV risk
Context of Use

- **Historical Assumptions**
  - 30 yrs ago, requirement to run 3yr, placebo-controlled trial against major coronary event outcomes (acute MI, stroke, CV death) with ~500+ patients per arm
  - Event rates were much higher
  - Not comparing trial where statin is SOC

- **Use Statement**
  - Level and change in serum LDL-C concentration reflects the long-term (5 year) rate of major coronary event outcomes and can be used to predict this outcome in a 6 month trial with #subject related to event rate, and trial arm(s).

- **Patient Populations**
  - Subjects between the ages of 40 and 70 (women and men, all racial background)

- **Other factors that will define the limits of the decision**
  - Clinical utility, sample size, subtypes, event rate
Benefit Assessment

Cardiovascular Biomarker

- **Primary prevention**
  - Outlier values of the CV biomarker could lead to the early identification of CV risk and the initiation of earlier therapeutic interventions of risk
  - Fewer people die, have a stroke or acute MI

- **Secondary prevention**
  - Given systemic nature of atherosclerosis, outlier values of CV biomarker could drive more aggressive therapeutic interventions to prevent subsequent events in the same or other vascular beds
  - Identification of additional mechanisms for reducing the risk of CV events
Risk Assessment

- Cholesterol level is only one of several CV risk factors and this measurement may not account for a change in risk for these other factors.

- A therapeutic that acts on one of the other factors will not be recognized as beneficial to CV event reduction.

Risk Mitigation

- What amount of risk is the patient population willing to take?
Figure 3. Risk of coronary heart disease according to levels of high-density lipoprotein-cholesterol; men aged 55, Framingham Study 24-year follow-up. CHD = coronary heart disease, SBP = systolic blood pressure, LDL = low-density lipoprotein, HDL = high-density lipoprotein.

In the search for an optimal therapy for avoiding or correcting atherosclerosis, the ideal lipid response would appear to be the one that raises HD lipoprotein as it lowers LD lipoprotein. Therapeutic maneuvers that affect only one of these lipoprotein particle systems in a favorable way, while adversely affecting the other, may be less promising than those that improve both the HD lipoprotein and LD lipoprotein values.

Removal of LDL via LDL-receptor
Removal of LDL via LDL-receptor

PCSK9 expression regulated by sterol regulatory element-binding Protein (SREBP)
Removal of LDL via LDL-receptor

Adapted from B Brewer

Partners for Innovation, Discovery, Health | www.fnih.org
LDL as a causal factor for atherosclerotic cardiovascular disease: key implications

- Cumulative LDL arterial burden is a central determinant for the initiation and progression of atherosclerotic cardiovascular disease.

- The lower the LDL cholesterol (LDL-C) level attained by agents that primarily target LDL receptors, the greater the clinical benefit accrued.

- Both proportional (relative) risk reduction and absolute risk reduction relate to the magnitude of LDL-C reduction.

- Lowering LDL-C in individuals at high cardiovascular risk earlier rather than later appears advisable, especially in those with familial hypercholesterolaemia.
Relationship between LDL-C and CV Events

Current Standard of Care to Lower LDL-C: Statins (Atorvastatin, Rosuvastatin Simvastatin, Pravastatin), Simvastatin/Ezetimibe

Relationship between LDL-C and CV Events


90,056 participants in 14 randomized trials of statins

Heterogeneity between statins or control and more intensive treatment
- before taking account of LDL difference: $\chi^2=37.41 (p<0.001)$
- after taking account of LDL difference: $\chi^2=4.5 (p=0.03)$
FDA Acceptance of LDL-C as Surrogate Endpoint

- LDL cholesterol reduction was the basis for FDA approval in 1987 of the first statin (lovastatin)
  - 7 years before the publication of the Scandinavian Simvastatin Survival Trial
  - The first trial to provide definitive evidence of a statin's clinical benefit.
  - Subsequent statin approvals were also based on the LDL cholesterol surrogate, as was approval of the first-in-class drug ezetimibe in 2002.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study Drug</th>
<th>Comparison</th>
<th>Primary End Point</th>
<th>% Difference in LDL Cholesterol Levels†</th>
<th>Cardiovascular Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>HERS</td>
<td>Estrogen (alone or in combination</td>
<td>Placebo</td>
<td>Nonfatal myocardial infarction or death due to coronary heart disease</td>
<td>−11</td>
<td>0.99 (0.80–1.22)</td>
</tr>
<tr>
<td></td>
<td>with medroxyprogesterone)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FIELD</td>
<td>Fenofibrate</td>
<td>Placebo</td>
<td>Nonfatal myocardial infarction or death due to coronary heart disease</td>
<td>−12</td>
<td>0.89 (0.75–1.05)</td>
</tr>
<tr>
<td>ILLUMINATE</td>
<td>Torcetrapib–atorvastatin</td>
<td>Placebo plus atorvastatin</td>
<td>Nonfatal myocardial infarction, stroke, hospitalization for unstable angina, or death due to coronary heart disease</td>
<td>−27</td>
<td>1.25 (1.09–1.44)</td>
</tr>
<tr>
<td>HPS-2 THRIVE</td>
<td>Niacin–laropiprant</td>
<td>Placebo</td>
<td>Nonfatal myocardial infarction, death from coronary causes, stroke, or arterial revascularization</td>
<td>−16</td>
<td>0.96 (0.90–1.03)</td>
</tr>
<tr>
<td>IMPROVE-IT</td>
<td>Ezetimibe–simvastatin</td>
<td>Placebo plus simvastatin</td>
<td>Death due to cardiovascular causes, nonfatal myocardial infarction, unstable angina requiring rehospitalization, coronary revascularization, or nonfatal stroke</td>
<td>−24</td>
<td>0.94 (0.89–0.99)</td>
</tr>
</tbody>
</table>

* CI denotes confidence interval, HERS Heart and Estrogen/Progestin Replacement Study, † FIELD Fenofibrate Intervention and Event Lowering in Diabetes, ‡ ILLUMINATE Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events, § HPS-2 THRIVE Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events, ‖ and IMPROVE-IT Improved Reduction of Outcomes: Vytorin Efficacy International Trial.

† The percent difference is for the comparison, during treatment, of the study drug with a placebo or another drug.
OSLER: 29 (0.9%) vs 31 (2.18%) events
PCSK9 inhibitors initially approved solely on the basis of LDL-C lowering

- Humanized MAbs inactivate proprotein convertase subtilisin–kexin type 9 (PCSK9)
  - Inactivation results in decreased LDL-receptor degradation, increased recirculation of the receptor to the surface of hepatocytes, and consequent lowering of LDL cholesterol levels in the bloodstream
  - Statins, by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, similarly act by increasing LDL-receptor expression

- This shared LDL cholesterol–lowering mechanism, combined with data on cardiovascular events from genetic studies of persons with PCSK9 gain- or loss-of-function mutations, provided the optimism of the likely cardiovascular benefits of these agents

- Both drugs were approved by FDA with LDL cholesterol reduction as the surrogate measure of clinical benefit. No efficacy data on cardiovascular outcomes were provided to the advisory committee

- Thus, the principal issue before the advisory committee was whether the observed LDL cholesterol reduction provided sufficient evidence to substitute for demonstration of clinical cardiovascular benefit.
OSLER: 29 (0.9%) vs 31 (2.18%) events
FOURIER: 1344 (9.8%) vs 1,563 (11.3%) events
LDL-C as a Surrogate Endpoint

Summary conclusions

- Links were established between lipids and cardiac end organ injury
- Over decades of research and innovation, refinements were made in the characterization of which cholesterol carrying lipoproteins were causally related to vascular injury
- The metabolism of those disease causing lipoproteins was subsequently characterized, permitting the identification of targets which would modify their circulating levels
- Over decades of research has shown that multiple approaches to reducing LDLc results in a reduction in CV events
- Subsequently randomized clinical trials confirmed that the modification of levels of LDL-C could reduce the occurrence rate of major cardiovascular events.
  - a reduction of 1 mmol per liter (38.7 mg per deciliter) in LDL cholesterol levels yields a consistent 23% reduction in the risk of major coronary events over 5 years
LDL-C and HDL-C and CV outcomes: The Framingham Study

Biomarker Evidentiary Framework

In Drug Development

Need Statement

COU

Benefit

Risk

What is the acceptable level of uncertainty?

Evidentiary Criteria

- Level and Δ in serum HDL concentration as a predictive biomarker of CV risk long-term (10 year) rate of major coronary event outcomes
- Predict risk in 6 month trial with 1000 subjects - related to event rate, and trial arm(s).
- All races, M/F, age 40-70

Primary prevention
- < deaths, stokes & acute MI
- Early ID of CV risk and initiation of therapeutic interventions

Secondary
- Drive more aggressive therapeutics, address systemic vascular comorbidities
- ID other mechanisms for reducing the risk of CV events

Cholesterol level is only one of several CV risk factors
- May not account for a Δ in risk for these other factors
A therapeutic that acts on one of the other factors will not be recognized as beneficial to CV event reduction

General
- Multiple LDL-C lowering drugs raise HDL levels
- CEPT deficient patient Subjects Have Increased HDL and Apo A1 Levels

Surrogate Endpoint
- Research has shown that elevating HDL opposes atherothrombosis
- The modification of HDL-C levels by CETP inhibition, in and of itself, does not appear to provide clinical benefit
- Subsequently randomized clinical trials confirmed that the modification of levels of HDL do not provide universal reduction in the occurrence rate of major cardiovascular events

Basically the same as LDL-C (or for other CVD factors)
Can we reduce risk BEYOND what statins have achieved?

Reduction in major coronary events vs. placebo (%)

*Includes stroke
†P≤0.0005
**P≤0.001

Potential for further risk reduction


Context of Use

Use Statement
- Level and change in serum HDL concentration reflects the long-term (10 year) rate of major coronary event outcomes (acute MI, stroke, CV death) and can be used to predict this outcome in a 6 month trial with 1000 subjects

Patient Populations
- Subjects between the ages of 40 and 70 (women and men, all racial background)

Other factors that will define the limits of the decision
- Clinical utility, sample size, subtypes, event rate
Benefit Assessment

Cardiovascular Biomarker

- **Primary prevention**
  - Outlier values of the CV biomarker could lead to the early identification of CV risk and the initiation of earlier therapeutic interventions of risk
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- Risk Mitigation

- What amount of risk is the patient population willing to take?
Major Clinical Trials to Elevate HDL-C: Reductions in Major Coronary Events

- CDP*: Coronary Drug Project
- VA-HIT: Veterans Affairs HDL-C Intervention Trial
- HHS: Helsinki Heart Study
- HATS: HDL-Atherosclerosis Treatment Study

<table>
<thead>
<tr>
<th>Treatment</th>
<th>CDP*</th>
<th>VA-HIT</th>
<th>HHS</th>
<th>HATS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niacin</td>
<td>-11</td>
<td>-22</td>
<td>-34</td>
<td>-90</td>
</tr>
<tr>
<td>Niacin + Simvastatin</td>
<td></td>
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<tr>
<td>Gemfibrozil</td>
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</table>

*Mortality only

Reduction in major coronary events (%)

CETP Deficient Subjects Have Increased HDL and Apo AI Levels

<table>
<thead>
<tr>
<th>Group</th>
<th>CETP ug/ml</th>
<th>Total HDL (mg/dl)</th>
<th>LDL (mg/dl)</th>
<th>HDL (mg/ml)</th>
<th>LDL (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homozyg.</td>
<td>0*</td>
<td>271*</td>
<td>164* (209%)</td>
<td>77* (-44%)</td>
<td>2.13* (72%)</td>
</tr>
<tr>
<td></td>
<td>(10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterozyg.</td>
<td>1.4*</td>
<td>195</td>
<td>66* (25%)</td>
<td>111 (-5%)</td>
<td>1.49* (20%)</td>
</tr>
<tr>
<td></td>
<td>(0.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>2.3</td>
<td>189</td>
<td>53</td>
<td>117</td>
<td>1.24</td>
</tr>
<tr>
<td></td>
<td>(10)</td>
<td></td>
<td></td>
<td></td>
<td>0.78</td>
</tr>
</tbody>
</table>


* Significant difference from Unaffected p<0.05
numbers in parathesis are % change
Mechanisms of HDL-C protection

- Reverse cholesterol transport
- Direct effects on vascular wall
Reverse Cholesterol Transport

The image illustrates the reverse cholesterol transport pathway. It shows the movement of cholesterol from peripheral tissues to the liver, where it is eventually excreted in feces. The process involves the following steps:

1. **VLDL (Very Low-Density Lipoprotein)**: Cholesterol is packaged into VLDL particles in the liver.
2. **IDL (Intermediate-Density Lipoprotein)**: VLDL particles are converted into IDL particles in the bloodstream.
3. **LDL (Low-Density Lipoprotein)**: IDL particles are further processed into LDL particles.
4. **LDL Recycling**: LDL particles are taken up by the liver and peripheral tissues.
5. **HDL (High-Density Lipoprotein)**: HDL particles are produced in the liver and circulate in the bloodstream.
6. **Reverse Transport**: HDL particles take up cholesterol from peripheral tissues and are taken up by the liver via the ABCG1 receptor.
7. **Bile Excretion**: Cholesterol is excreted in the bile and eventually eliminated in feces.

Key Players:
- **ABCG-1**: A transport protein involved in cholesterol export from cells.
- **SR-A**: Scavenger Receptor A, involved in the uptake of LDL particles.
- **CD36**: A protein involved in the uptake of fatty acids and lipids by macrophages.

The diagram also highlights the role of oxidation in lipid metabolism and the importance of the arterial wall in the overall process.
Cholesteryl ester transfer protein (CETP)
Cholesteryl ester transfer protein (CETP)
ILLUMINATE™ Trial
Clinical outcomes in subjects with CHD or risk equivalents

Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events

atorvastatin run-in to LDL <100 mg/dL (2.6 mmol/L)
4-10 weeks

15,067

torcetrapib + titrated atorvastatin dose
Planned 4.5 years of treatment
titrated atorvastatin dose

On Dec 2, 2006, after a median follow-up on-treatment of 550 days:
• Prematurely terminated based on the totality of evidence
• Statistically significant excess of deaths (which crossed the pre-defined statistical boundary) and cardiovascular events in the group treated with torcetrapib

ILLUMINATE™ Trial: Estimated Hazard Ratios:
All-cause mortality and Major Cardiovascular Events (MCVE)

**All-cause mortality**

- **All-cause mortality**
  - HR = 1.58 (1.14, 2.19) p = 0.006
  - Atorvastatin (A) deaths = 59
  - Torcetrapib/Atorvastatin (T/A) deaths = 93

**Major Cardiovascular Events**

- **Major Cardiovascular Events**
  - HR = 1.25 (1.09, 1.44) p = 0.001
  - Atorvastatin (A) events = 373
  - Torcetrapib/Atorvastatin (T/A) events = 464


**Lipids**
- HDL-C
  - T/A + 72%
  - A + 2%

- LDL-C
  - T/A - 22%
  - A + 1%
### CETP inhibitors: Clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>Torcetrapib 60 mg (12 mo)</th>
<th>Dalcetrapib 900 mg (4 week)</th>
<th>Anacetrapib 150 mg (4 week)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Δ HDL</td>
<td>+ 72%</td>
<td>~ + 34%</td>
<td>~ + 80%</td>
</tr>
<tr>
<td>% Δ LDL</td>
<td>- 25%</td>
<td>~ - 7%</td>
<td>~ - 35%</td>
</tr>
<tr>
<td>Δ SBP</td>
<td>+5.5 mmHg</td>
<td>not reported</td>
<td>+ 0.6 mmHg</td>
</tr>
<tr>
<td>Aldosterone pre-clinical</td>
<td>+</td>
<td>?</td>
<td>-</td>
</tr>
</tbody>
</table>
Dalcetrapib
HDL-C and LDL-C by treatment group

N=15,871
Data are mean ± 95% CI

Dalcetrapib
Primary outcome* by treatment group

* Coronary heart disease death, non-fatal MI, ischemic stroke, hospitalization for unstable angina, resuscitated cardiac arrest

## Anacetrapib
### HDL-C and LDL-C by treatment group

| Lipid or Lipoprotein | Anacetrapib \(N = 15,225\) | Placebo \(N = 15,224\) | Absolute Difference\(\dagger\) | Relative Difference
<table>
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<tr>
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</thead>
<tbody>
<tr>
<td>Mean LDL cholesterol (mg/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct method</td>
<td>38</td>
<td>64</td>
<td>-26</td>
<td>-41 percent</td>
</tr>
<tr>
<td>Beta quantification(\ddagger)</td>
<td>53</td>
<td>63</td>
<td>-11</td>
<td>-17 percent</td>
</tr>
<tr>
<td>Mean non-HDL cholesterol (mg/dl)</td>
<td>79</td>
<td>96</td>
<td>-17</td>
<td>-18 percent</td>
</tr>
<tr>
<td>Mean HDL cholesterol (mg/dl)</td>
<td>85</td>
<td>42</td>
<td>43</td>
<td>104 percent</td>
</tr>
<tr>
<td>Mean apolipoprotein A1 (mg/dl)</td>
<td>160</td>
<td>118</td>
<td>42</td>
<td>36 percent</td>
</tr>
<tr>
<td>Mean apolipoprotein B (mg/dl)</td>
<td>54</td>
<td>66</td>
<td>-12</td>
<td>-18 percent</td>
</tr>
<tr>
<td>Mean triglycerides (mg/dl)</td>
<td>136</td>
<td>146</td>
<td>-10</td>
<td>-7 percent</td>
</tr>
<tr>
<td>Mean lipoprotein(a) (nmol/liter)</td>
<td>43</td>
<td>58</td>
<td>-15</td>
<td>-25 percent</td>
</tr>
</tbody>
</table>

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Anacetrapib
Primary outcome* by treatment group

* Coronary heart disease death, non-fatal MI, or coronary revascularization

HDL-C as a Surrogate Endpoint

Summary conclusions

- While HDL-C is an appears to be an established epidemiologic predictor of CV risk, the modification of HDL-C levels by CETP inhibition, in and of itself, does not appear to provide clinical benefit.

- The modest CV risk reduction seen in the REVEAL study can be accounted for by the additional LDL-C and non-HDL-C lowering.

- Non-acceptance of HDL-C as a surrogate endpoint and requiring further clinical trial evidence was the appropriate action.
The identification of cholesterol as a causal agent of vascular injury, in both man, and some animals, was the foundation for its eventual acceptance as a surrogate biomarker of risk.

With the identification of subsets of lipoproteins that transported circulating cholesterol, as predictive of cardiovascular risk, it became feasible to attempt to modify their levels, in the assessment of safety and efficacy of potential treatments.

It subsequently became possible to demonstrate the dose related efficacy of novel lipid modifying agents which showed a direct correlation between the level of the circulating biomarker (LDL-C) and clinical outcomes.

This same paradigm for biomarker validation revealed the failure of HDL-C to meet the same standard as a surrogate of clinical benefit.
Question and Answer Session

■ LDL lowering has been shown to reduce risk of cardiac events with several different mechanisms.
  • Do you think there is sufficient proof of universality or should the regulators require post marketing studies to proof the reduction in cardiac events?

■ Increasing HDL has not been accepted as a surrogate for cardiovascular benefit.
  • Important to understand different mechanisms & effects on a surrogate (safety vs. efficacy)
    o i.e. Impacts of negative outcome of increased BP with Torcetrapib

■ Does a single neutral or negative correlation to outcome eliminate potential for surrogacy?
  • Increase HDL (i.e. different class) - what is required or what additional evidence is needed?

■ Influence of approved drugs on future decision-making?
  • PCSK9 was given a fairly broad label with approval
  • Would future drugs (classes) with strong genetic causality be treated similarly?

■ Could the elevation of HDL and reduction of LDL “in combination” be a possible surrogate?

■ Strength of Causality (robust genetics) & Plausibility (inference of correlations to outcomes)
  • Different weights applied to level of evidence